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RESEARCH ARTICLE

Randomized, controlled clinical trial of acoustic stimulation to reduce postconcussive symptoms

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Abstract

Objective: Effective interventions are needed to address postconcussive symptoms. We report the results of randomized, sham-controlled trial of Cereset Research™ Standard Operating Procedures (CR-SOP), a noninvasive, closed-loop, allostatic, acoustic stimulation neurotechnology previously shown to improve insomnia. **Methods**: Military service members, veterans, or their spouses with persistent symptoms (Neurobehavioral Symptom Inventory [NSI] Score ≥23) after mTBI 3 months to 10 years ago, were randomized to receive 10 sessions of engineered tones linked to brainwaves (LB, intervention), or random engineered tones not linked to brainwaves (NL, sham control). The primary outcome was change in NSI, with secondary outcomes of heart rate variability and self-report measures of sleep, mood, and anxiety. **Results**: Participants (n = 106, 22% female, mean age 37.1, 2.8 deployments, 3.8 TBIs) were randomized 1:1 to LB or NL, with no significant differences between groups at baseline. Among all study participants, the NSI declined from baseline 41.0 to 27.2 after ($P < 0.0001$), with gains largely sustained at 3 months (31.2) and 6 months (28.4). However, there were no significant differences between the LB (NSI declined from 39.9 at baseline to 28.2 post-intervention, 31.5 at 3 months, and 29.4 at 6 months) and NL (NSI declined from 41.5 at baseline to 26.2, 29.9, and 27.3, respectively. Similar patterns were observed for the PCL5 and PHQ-9 and there was no difference in HRV between groups. **Interpretation**: Ten hours of acoustic stimulation while resting in a zero-gravity chair improves postconcussive symptoms. However, linking tones to brain electrical activity did not reduce symptoms more than random tones. Registration: ClinicalTrials.gov – NCT03649958

Introduction

Mild traumatic brain injury (mTBI), also known as concussion, has been reported in over 370,000 United States military service members (SMs) since 2000.[1] The actual number may be higher due to underreporting and lack of documentation. Though most SMs recover within 7–30 days, approximately 15% of those sustaining concussion experience persistent postconcussive symptoms (PPCS) at least 3 months post-injury.[2] PPCS include a wide range of cognitive, emotional, physical, and functional symptoms. Even with the end of combat operations in Iraq and Afghanistan, it is predicted that at least 20,000 new cases of TBI will occur annually among service members in non-deployed environments.[3] Military veterans with persisting symptoms after TBI report lower quality of life than demographically matched veteran controls,[4] and both military personnel and civilians may

be at higher risk for development of addiction-related disorders after TBI.[5–7] For many individuals, without effective treatment the symptomatic and functional sequelae of mTBI are likely to persist or even become permanent.[8] This underscores the need to identify safe and efficacious interventions to facilitate recovery from TBI-related symptomatology.

Current mTBI treatment is primarily focused on education, symptom management, and graded return to activity during the acute injury period (<30 days). For PPCS, a multidisciplinary evaluation and symptom-focused care approach are employed. In addition to the common PPCS like headaches, cognitive complaints, vestibular issues, and emotional disturbances, there are many common comorbid conditions that frequently occur, including sleep disturbances, psychological distress (e.g., posttraumatic stress symptoms, anxiety, depression), and musculoskeletal pain. These comorbidities can complicate evaluation, treatment, and recovery. Therefore, novel therapies that also target potential physiological underpinnings for PPCS are needed. One promising area for such novel treatments is targeting the autonomic nervous system (ANS).

The ANS is comprised of the sympathetic and parasympathetic nervous systems, which work in tandem to maintain a physiological homeostasis. Increasing evidence indicates autonomic dysfunction is common after mTBI and could underlie many PPCS.[9] For some individuals, mTBI may induce autonomic dysfunction that in turn disrupts physiological homeostasis. This then causes either hyperarousal or hypoarousal, which can result in PPCS-like symptoms. Prior research[10] documents disruption in ANS physiological markers, including heart rate, heart rate variability, blood pressure, and cerebral blood flow (Fig. 1) after mTBI, particularly in the acute injury phase and when engaged in physiologic challenges or exertional tasks.[9] Therefore, interventions that target autonomic dysfunction may prove effective for PPCS.

Understanding of the ANS has primarily focused on anatomically inferior neural structures or body tissues, including the brainstem, hypothalamus, spinal ganglia, vagus nerve, adrenal glands, circulating neurotransmitters, and cellular receptors of end-organs. There is increasing appreciation for how the ANS is regulated by pathways of the central nervous system that are anatomically and functionally more "upstream."[11–13] At the level of the cerebral hemispheres, one intriguing, relatively unexplored finding is that the two hemispheres make differential contributions to management of the sympathetic and parasympathetic divisions.[14,15] TBI may induce autonomic dysregulation through predominantly asymmetrical activity in homologous regions of the cerebral hemispheres responsible for managing the ANS. This bihemispheric autonomic model (BHAM) postulates that acute trauma, whether physical or emotional, may trigger a sympathetic, high-arousal, fight-or-flight response. If this response is allowed to persist, it could be associated with dominant and maladaptive asymmetrical activation in regions of the brain responsible for autonomic management, especially the bilateral insulae in the vicinity of the temporal lobes.[15]

An implication of the BHAM is that interventions fostering greater symmetry or "balance" may facilitate recovery from lateralizing effects of TBI, enabling more optimal levels of sympathetic and parasympathetic activation. Neurotechnologies (i.e., therapeutic systems that impact neurological functioning) have the potential to impact brain activity in this manner. Many of these technologies are open-loop and akin to biofeedback approaches, requiring active manipulation by the recipient. Others are closed-loop, where the recipient is passive throughout the intervention. Closed-loop technologies are believed to impact neural circuits through real time monitoring and calibrated intervention, resulting in highly individualized dynamic therapeutic adjustments in brain activity, via the principles of allostasis.[16] Allostasis refers to "stability through change." This advanced model of physiological regulation recognizes that in health, operational "set points" undergo constant recalibration, depending on prevailing and anticipated needs of the natural environment.[17–19] Past work with one intervention using the principle of allostasis, HIgh-resolution, Relational, Resonance-based Electroencephalic Mirroring (HIRREM®), has shown promise at reducing symptoms of insomnia, posttraumatic stress symptoms, depression, and anxiety, as well improving autonomic cardiovascular regulation.[20–30]

Cereset Research™ (CR) is an upgraded version of HIRREM that rapidly echoes brainwaves in real time as audible engineered tones in a closed-loop paradigm (Fig. 2). This technology is available commercially as a general wellness device for relaxation, well-being, and stress management, and has an FDA exemption. Application of CR with computer algorithm standard operating procedure (CR-SOP) eliminates the potential for human error and improves speed in translating and reflecting brainwaves as tones.[31]

The objective of our study was to evaluate the efficacy of CR-SOP in reducing symptoms that persist at least 3 months after injury. We hypothesized that 10 sessions of CR-SOP would result in greater self-reported symptom reduction than 10 sessions of sham nonspecific acoustic stimulation, and that these gains would persist at least 3 months post-intervention. We further explored the impact of CR-SOP on other behavioral and autonomic measures.

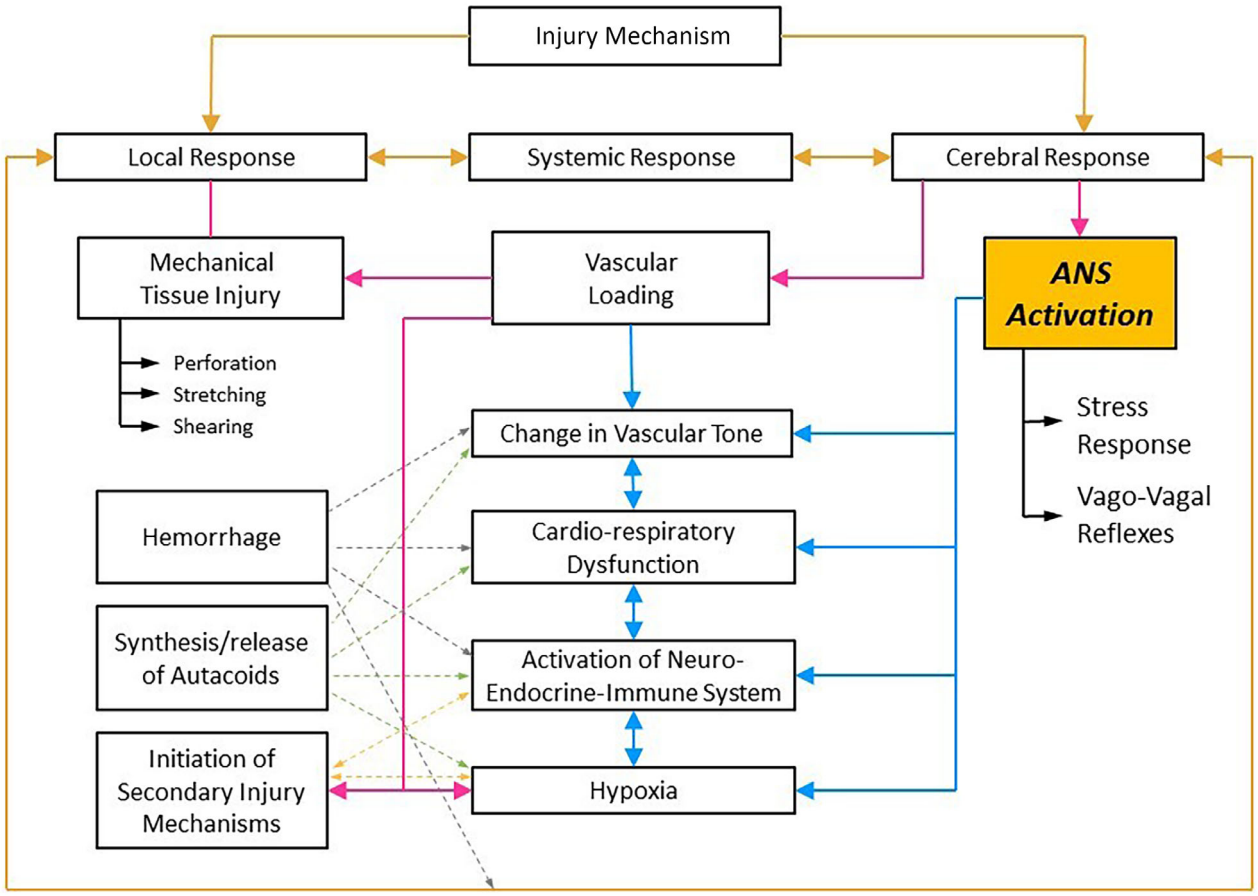

Figure 1. Cerebral, systemic, and local responses to blast-induced neurotrauma. Adapted from Cernak and Noble-Haeusslein, 2010.

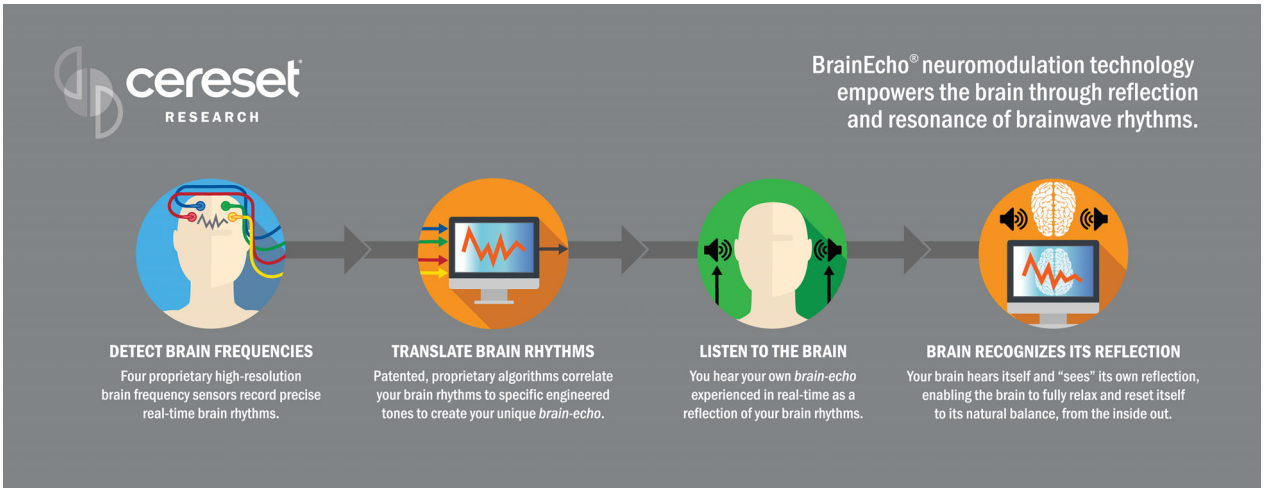

Figure 2. Overview of CR-SOP closed-loop acoustic stimulation neurotechnology for auto-calibration of neural oscillations.

Methods

Study participants

This multisite, randomized controlled trial was conducted at Uniformed Services University/Walter Reed National Military Medical Center in Bethesda, MD and Womack Army Medical Center at Fort Bragg (now Fort Liberty), NC. Participants were active duty service members, retired veterans, or military dependents with a history of traumatic brain injury at least 3 months, and no more than 10 years, prior; this interval was chosen to avoid those in the acute period who might be likely to spontaneously recover from their TBI-related symptoms on the one hand, and to cover TBIs likely to have occurred during their military service years, while avoiding a significant focus on TBIs that may have occurred in childhood or adolescence. It should be noted that all were eligible for care in the Department of Defense healthcare system, which may at least in part offset issues related to socioeconomic status and access to care that may be of concern in other settings. They were required to have likely PPCS that resulted in a score of ≥23 on the Neurobehavioral Symptom Inventory (NSI). History of TBI was confirmed by the administration of the Ohio State University TBI Identification Method Interview. Other inclusion criteria included willingness to abstain from alcohol or recreational drugs during the intervention phase and for at least 3 weeks after completion of the intervention. They were asked to discontinue for at least five half-lives prior to initiation of the study and during study participation any medications in the following classes: benzodiazepines, opioids, antipsychotics, mood-stabilizers, anticonvulsants, non-benzodiazepine sleep aids, prescribed sedative-hypnotics, and medical marijuana or cannabinoid medication. They were also asked to avoid initiation of them during the period of study participation. Discontinuation or delayed initiation of any treatments prior to study participation was done with concurrence and guidance from the individual's treating providers, utilizing a washout period of at least five half-lives of the medication in question before initiating baseline assessment and intervention. Participants were excluded if they reported a history of moderate or severe TBI, had a diagnosis of a psychotic disorder, severe depression (score ≥20 on the PHQ-9), bipolar disorder, current alcohol or substance use disorder, or had active suicidal or homicidal ideation. Hearing difficulties that impaired hearing normal conversational volume was exclusionary. Recruitment at USUHS/Walter Reed and Fort Bragg was through informational tables, physician referral, and word of mouth, as well as via social media and local news stories.

Study design

This is a prospective double-blind, two-arm, randomized controlled clinical trial. After the completion of written informed consent and baseline assessments, participants were randomly allocated 1:1 to intervention or a random tones control using blocked randomization with a block size of 4. The randomization scheme was created by an investigator having no contact with the participants. With the exception of the Technologist, all other research staff were blinded to group assignment. Participants were blind to treatment group until completion of the final follow-up assessment.

Fifty participants were randomized to CR-SOP of acoustic stimulation with computer engineered tones linked to brainwaves (LB, intervention), and 54 to CR-SOP with random engineered tones not linked to brainwaves (NL, control). The target enrollment, after attrition, was least 42 per group to allow 80% power, based on pilot studies and a priori power analyses. All study procedures were approved by the Uniformed Services University institutional Review Board (IRB) as the primary IRB of record, with secondary approval from Walter Reed's IRB and Womack Army Medical Center's Human Research Protection Program.

Sessions began 0–14 days following the V1 enrollment visit. All participants received 10 sessions over 1–5 weeks. Participants could complete two sessions in a single day, with at least a 60-min break between sessions. Participants were encouraged to complete all 10 sessions as close together as possible to maximize benefit based on previous work[30] (ideally over 1–2 weeks), but sessions were scheduled at participants' convenience. More than 5 days between sessions was considered a break in sessions.

All study assessments were repeated at 0–14 days (V2), 3 months (V3, the study's a priori primary endpoint), and 6 months (V4) post-intervention. Assessments had a ±2 week window for completion. Due to COVID-19 closures, in-person study activity was not possible for several months in 2020, resulting in breaks or withdrawals for some in the intervention phase, with some subsequent assessments being delayed, or conducted remotely, and consequently limited to questionnaires.

Closed-loop neurotechnology intervention

The CR-SOP intervention features 10 sessions, each lasting approximately 60–75 min. During each session, paired electrodes are placed symmetrically at predetermined scalp locations, targeting the bilateral hemispheres according to the 10–20 International System. Each session includes 4–6 protocols. Individual protocols last

from 6 to 20 min; total intervention listening time is 536 min.

All participants were instructed to close their eyes and relax while sitting in a chair (Human Touch PC-6), adjusted to their preferred level of recline. Participants passively listened to audible tones via earbud-style headphones as they relaxed or even fell asleep. Tones were computer engineered with regard to the timing and intensity of the phases of the musical notes, which include attack, decay, sustain, and release. Participants in the intervention group (LB) received tones linked in real time to dominant frequencies while the control group (NL) received randomly generated tones unrelated to brain activity as a sham active control intervention. All interactions, procedures, sensor placements, and session times for NL mirrored the intervention LB condition. A more detailed description of the CR-SOP intervention has been published.[31]

Study procedures

After providing informed consent, participants received a baseline assessment (V1) and were then randomized into CR-SOP LB or NL. They then completed the 10 sessions. Post-treatment assessment (V2) occurred within 14 days after the final treatment session. Assessments were repeated at 3 months (V3) and 6 months (V4), ±2 weeks, after completion of the intervention (Fig. 3).

Safety and adverse events

Participants were informed of potential adverse events, including skin irritation from electrode paste, and transient paradoxical effects (e.g., lighter sleep, vivid dreams) which occur in <15% of participants. Prior to each session, participants were asked about changes to their health, including new or worsened symptoms. Safety monitoring was conducted by the site Principal Investigators, with consultation with the study Principal Investigator or Medical Monitor as needed.

Data management

Data security measures consistent with DoD standards were implemented to prevent inadvertent disclosures. All participant data were de-identified and locally stored on secure computer systems and with paper files double locked. Coded data were entered by approved research study staff into a centralized secure database managed by the Center for Neuroscience and Regenerative Medicine's Informatics Core at the Uniformed Services University.

Outcome measures

A series of self-reported outcome measures and continuous recordings of HR were collected at the V1 and subsequent follow-up visits. The primary outcome in this study

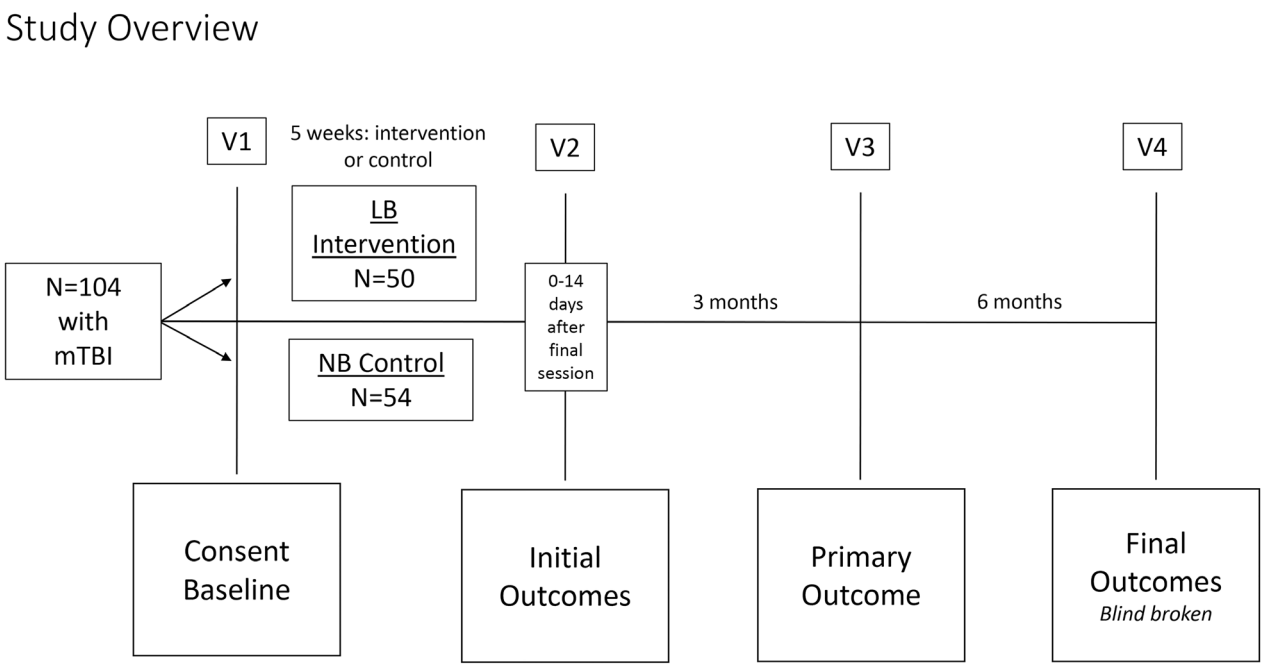

Figure 3. Study overview demonstrating timeline for visits, intervention/control delivery, and outcome collection during the randomized (Visits 1–4).

was differential change in the score reported on the NSI from V1 to V3 (baseline to 3 months post-intervention completion).

Psychological and psychophysiological function

mTBI symptoms clusters

The NSI is a 22-item self-report questionnaire of neurobehavioral symptoms with a scale from 0 (none) to 4 (very severe) and a total score range from 0 to 88.[32] The NSI is used by the DoD and Department of Veterans affairs for TBI research and clinical evaluation.[33]

Insomnia

The Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI) self-report aspects of sleep. The ISI addresses insomnia, with responses from 0 to 4 for each of 7 questions, total score range 0–28.[34] The PSQI is a 19-item inventory assessing past month sleep quality with items in 7 categories weighted on a 0–3 scale. A global PSQI score is calculated by totaling the seven component scores, providing 0–21 range, where lower scores denote healthier sleep quality.[35]

Stress

The PTSD Checklist for DSM-5 (PCL5) is a validated 20-item self-report measure of posttraumatic stress symptom severity.[36,37] Each symptom is rated from "Not at all" (0) to "Extremely" (4), for a total range of 0–80 with higher score indicating greater severity.

Pain

The Headache Impact Test (HIT-6) is a validated measure of headache impact on work, school, home, and social function featuring six questions ranging from never (scored as 1) to always (5). Total headache impact is categorized from little or none to severe.[38]

Depression

The Patient Health Questionnaire (PHQ9) is a validated questionnaire for measuring depression severity. Nine items ranging from 0 to 3 (not at all to nearly every day) yield total scores of 0–27.[39,40]

Expectation measure

Participants were asked if they believed they were assigned to acoustic stimulation linked to brainwaves (LB) or non-specific acoustic stimulation (NL). This was obtained at V1, and before the fifth session to assess the efficacy of blinding, as well as at V3 and V4.

Heart rate (HR) and heart rate variability (HRV)

Continuous HR recordings were obtained from participants completing assessments in person using the Faros 180 heart rate monitor (Bittium Corporation, Oulu, Finland) at V1, V2, V3, and V4. The participant was comfortably seated for 10 min during recordings. Beat to beat intervals (RRI) files were generated at 1000 Hz via the data acquisition software. Files were analyzed with Nevrokard HRV software (Nevrokard Kiauta, d.o.o., Izola, Slovenia) following published methods to exclude artifact then utilize the first 5 min of quality tracings to derive measures of heart rate variability (HRV) including integration over specified frequency ranges (LF: 0.04–0.15 Hz; HF: 0.15–0.4 Hz), standard deviation of NN Intervals (SDNN), and root mean square of successive differences.[41]

Reaction time and balance

The Automated Neuropsychological Assessment Metrics (ANAM) subtests for simple reaction time and procedural reaction time were obtained at V1, V2, V3, and V4. Balance was assessed with the modified balance error scoring system (mBESS) at V1, V2, V3, and V4.[42]

Statistical analyses

Data were analyzed using SAS software (SAS Version 9.4) and R software (R Version 4.2.1). To ensure group equivalency, baseline characteristics were compared using two-sample, two-tailed *t*-tests (continuous variables) and chi-squared and/or Fisher's exact test (categorical variables). Linear mixed effects (LME) models were applied to assess change over time for primary and secondary outcome measures. Additionally, these models were applied to assess change over time in these measures between the two treatment arms (i.e., change from baseline to V2, V3, and V4, respectively). The primary outcome measure of interest was change in mean NSI from baseline to V3. Each model included a random effect for subject to account for within-subject correlation in the measures over time. Similar analyses were conducted to examine change over time in HRV measures. Two-sided tests and a significance level of 0.05 were assumed. Analyses were conducted as intention-to-treat (ITT). Given that descriptive results indicated negligible differences in the means of the different outcome measures at all visits for the ITT and per-protocol analytic samples, no per-protocol analyses were conducted. Because the descriptive results

indicated negligible differences between the ITT and per-protocol samples, missing data occurring at follow-up were assumed to be missing at random. LME analysis accounts for data that are missing at random. No further sensitivity analyses regarding missing data were conducted. Given an absence of significant treatment group differences with respect to baseline characteristics, no sensitivity analyses were done regarding baseline variables for treatment and time effects in the models.

Results

Sample demographics

A total of 118 subjects were assessed for eligibility. The target number of 106 eligible participants were consented and enrolled. Two participants dropped our prior to randomization. Randomization of 104 participants yielded no significant differences between the two groups at baseline (Fig. 4). The mean age of participants was 37.2 (SD: 10.8) years; 21% were women. Demographic, military status and history, clinical comorbidities, and prior therapeutic modalities were similar between groups (see Tables 1–4), and are similar to the overall military population. The majority of TBIs for this cohort were caused by explosions, fights, falls, and/or crashes.

Time over which sessions were completed and intervals to data collection time points were similar for both groups. There were no significant differences between groups for the total days over which the intervention was completed (LB: 17.60 (SD: 8.12) days and NL: 18.69 (SD: 8.98) days), in-office days receiving sessions (LB: 7.40 (SD: 2.24) days and NL: 7.54 (SD: 2.32) days), days between V1 and the start of sessions, number of breaks in sessions (LB – 22 participants had at least one break in sessions, 10 had at least two breaks, 1 had three breaks and NL – 27 participants had at least one break in sessions, 12 had at least two breaks, 1 had three breaks), or days between last session and V3. Both groups were comparable with self-report relaxing and falling asleep during course of sessions (LB: 92%, NL: 93%). COVID-19 restrictions and lost data impacted both groups similarly, as 4 LB participants and 1 NL participant had data collected under COVID-19 adjusted protocols. For virtual visits resulting from COVID-19, questionnaire data, but no physical measures, were obtained. Recordings were adequate for HRV analysis compared to baseline in 68 participants at V3, and 56 at V4.

Participation

Of the 104 participants randomized, 50 were assigned to the intervention and 54 to the control group; all were included in intention-to-treat analyses. Of those assigned to intervention, 45 completed all sessions (3 discontinued due to time commitment, 1 discontinued due to nightmares, and 1 received only nine sessions due to the COVID-19 pandemic). In the control group, 49 completed all 10 sessions (2 discontinued due to time commitment, 2 due to COVID-19 pause, and 1 no show).

Outcomes

Primary outcome

Among all study participants, NSI improved significantly from a mean of 40.89 before intervention to 27.17 after (mean change: −13.72, 95% CI: −16.37 to −11.07), with improvement sustained at 3 months (mean: 30.18) and 6 months (mean: 27.88) (Fig. 5). However, the change in NSI score did not differ significantly by intervention group. In the LB group, mean NSI declined from 40.34 at baseline to 27.93 post-intervention, 30.41 at 3 months, and 28.53 at 6 months. In the NL group, mean NSI declined from 41.39 at baseline to 26.44 post-intervention, 29.96 at 3 months, and 27.25 at 6 months. Differences between LB and NL groups in change in mean NSI score from baseline were 2.54 (95% CI: −2.77 to 7.85) at post-intervention; 1.50 (95% CI: −3.95 to 6.95) at 3 months; and 2.33 (95% CI: −3.33 to 7.99) at 6 months.

Secondary outcomes

PTSD symptom severity, as measured by the PCL5, demonstrated more modest improvement post-intervention compared to baseline, achieving statistical but not clinical significance, which was sustained at 3 and 6 months. Depression symptom severity (PHQ-9), insomnia (ISI) and sleep quality (PSQI), heart rate variability (standard deviation of NN Intervals or the root mean square of successive differences methods), ANAM-4 simple reaction time and procedural reaction time, and the M-BESS did not demonstrate any significant differences from baseline or between treatment allocation groups at any time point (Figs. 6A–D, 7A–D, and 8A, B).

Adequacy of blinding

At V1, roughly 70% in both treatment arms believed they were randomized to the linked to brainwave group, $P < 0.97$. At S5, 62% in LB versus 51% (roughly 50–50) NL, thought they were randomized to the active arm, $P < 0.40$. At V3, 63% in LB versus 43% in NL thought they were randomized to the active arm, $P < 0.10$. This indicates adequate blinding based on expectation measure across time.

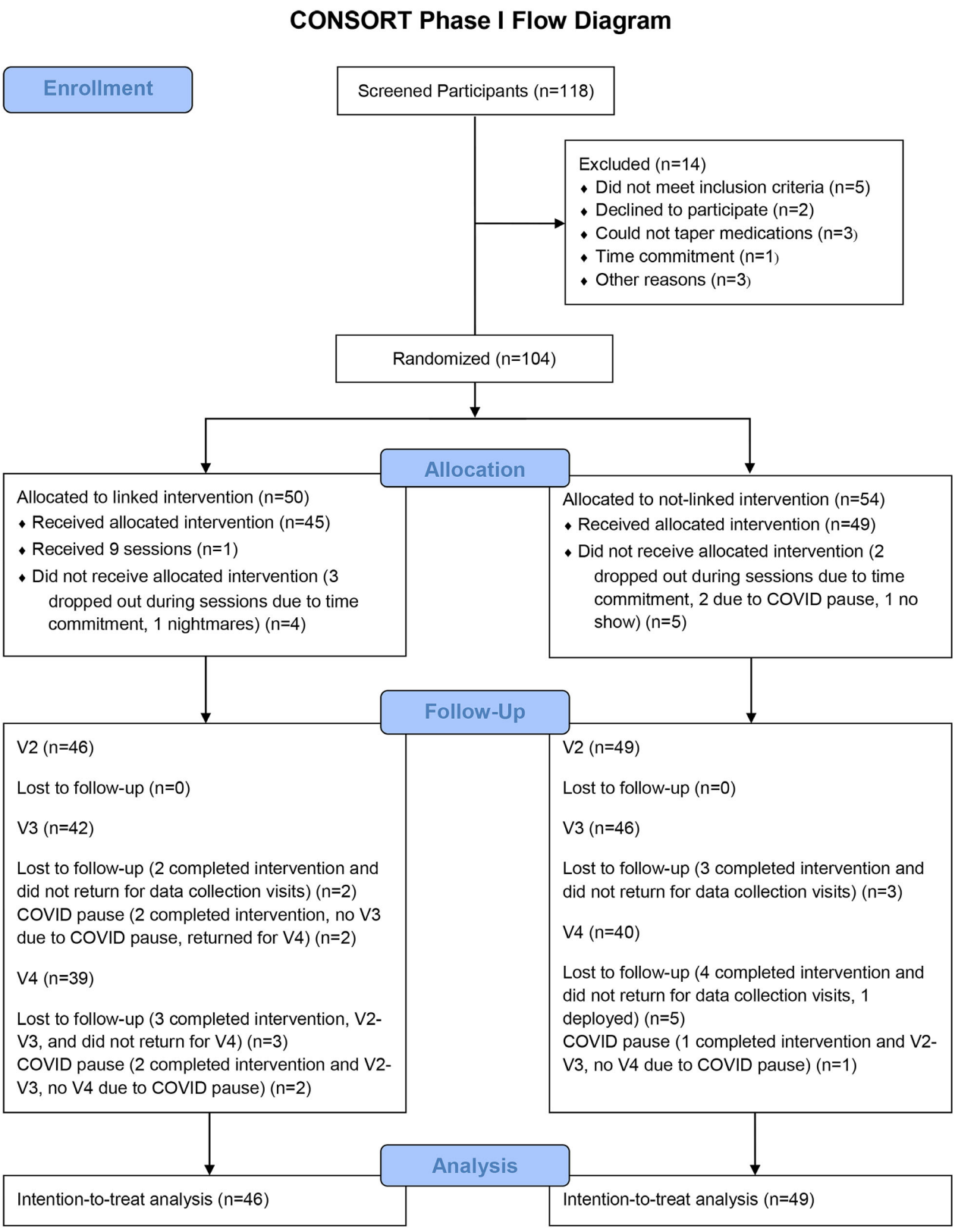

Figure 4. Consort diagram showing the flow of participants through the study for the groups receiving tones linked to brainwaves (LB, intervention), and tones not linked to brainwaves (NL, control).

Table 1. Participant demographics.

Variable	Intervention group (*N* = 50)	Control (*N* = 54)	*P*-value
Age, mean (SD), years	37.1 (10.9)	37.2 (10.7)	0.91
Male, *N* (%)	40 (80.0)	42 (77.8)	0.78
Race, *N* (%)			
White	36 (72.0)	29 (53.7)	0.13
Black	8 (16.0)	10 (18.5)	
Hispanic	1 (2.0)	8 (14.8)	
Asian	2 (4.0)	2 (3.7)	
Other	2 (4.0)	1 (1.9)	
Multiracial	1 (2.0)	4 (7.4)	
Marital status, *N* (%)			
Single	7 (14.0)	12 (22.2)	0.30
Married	34 (68.0)	35 (64.8)	
Separated	3 (6.0)	5 (9.3)	
Divorced	6 (12.0)	2 (3.7)	
Education, *N* (%)			
High school	5 (10.0)	10 (18.5)	0.48
Some college	9 (18.0)	15 (27.8)	
Associates degree	20 (40.0)	17 (31.5)	
Bachelors degree	4 (8.0)	3 (5.6)	
Advanced degree	11 (22.0)	9 (16.7)	
Missing	1 (2.0)	0 (0.0)	

P-values based on chi-squared or Fisher's exact test (categorical variables) and *t*-tests (continuous variables). Missing data categories not included. *P*-values reflect differences between treatment arms for participant characteristics.

Table 2. Participant employment and military service history.

Variable	Intervention group (*N* = 50)	Control (*N* = 54)	*P*-value
Employment status, *N* (%)			
Active duty	40 (80.0)	46 (85.2)	0.76
Retired/veteran	8 (16.0)	6 (11.1)	
Civilian	2 (4.0)	2 (3.7)	
Rank category, *N* (%)			
E1–E3	1 (2.0)	6 (11.1)	0.26
E4–E6	18 (36.0)	19 (35.2)	
E7–E9	14 (28.0)	14 (25.9)	
O1–O3	8 (16.0)	3 (5.6)	
O4–O6	3 (6.0)	4 (7.4)	
W1–W4	2 (4.0)	4 (7.4)	
Missing	4 (8.0)	4 (7.4)	
Branch, *N* (%)			
Army	37 (74.0)	42 (77.8)	0.49
Navy	7 (14.0)	9 (16.7)	
Marine corps	1 (2.0)	0 (0.0)	
USAF	1 (2.0)	0 (0.0)	
Coast guard	1 (2.0)	0 (0.0)	
Missing	3 (6.0)	3 (5.6)	
Number of times deployed			
Mean (SD)	4.0 (4.7)	3.7 (4.0)	0.72
Missing, *N*	3	3	
Number of months deployed			
Mean (SD)	20.7 (20.6)	24.2 (21.0)	0.42
Missing, *N*	4	5	
Years of active duty			
Mean (SD)	12.8 (7.4)	13.6 (7.8)	0.61
Missing, *N*	4	4	

P-values based on chi-squared or Fisher's exact test (categorical variables) and *t*-tests (continuous variables). Missing data categories not included. *P*-values reflect differences between treatment arms for participant characteristics.

Discussion

In this double-blind, two-arm, randomized controlled clinical trial, individuals with a history of mTBI and with persistent symptoms collectively demonstrated clinically and statistically significant reduction in postconcussive symptom severity after the completion of 10 study sessions. However, there was no difference in the improvement achieved by those randomized to closed-loop acoustic stimulation versus those receiving random, computer-generated acoustic stimulation. No intervention has yet proven efficacious in addressing the full sequelae of postconcussive symptoms, making this one of the more challenging medical conditions to try to address. The majority of participants had also tried at least one therapeutic modality before enrolling (Table 4). Examples of therapies tried include alpha stim, biofeedback, cognitive behavioral therapy (CBT), neurofeedback, attending the National Intrepid Center of Excellence (NICoE), eye movement desensitization and reprocessing (EMDR), omega 3 supplements, other relaxation therapies, service dog, stellate ganglion blocks, or transcranial magnetic stimulation (TMS). TBI recovery is complex and can be influenced by a variety of factors such as social support, sex, and socioeconomic status.[43–45] The fact that the overall study population showed such marked and sustained improvement indicates that study participation, which included relaxation via resting in a comfortable, zero-gravity chair with eyes closed in dim light while listening to engineered auditory tones, is therapeutic. Two previously published studies evaluating legacy HIRREM[30] and CR-SOP[31] for insomnia found improvement in both allocation groups, though the active intervention group had statistically significant larger improvement than the sham group. The intervention group in both studies also demonstrated clinically relevant improvement, whereas the sham groups did not. In the CR-SOP insomnia study, not only did sleep quality improve, but some measures of autonomic function improved significantly among the intervention group compared to control.[31] These studies, taken with the results of the current study, suggest the impact of the common elements between the allocation groups, notably 10 h of relaxation facilitated by a zero gravity chair and computer-generated auditory tones,

Table 3. Participant TBI and medical history.

Variable	Intervention group (*N* = 50)	Control (*N* = 54)	*P*-value
Number of TBIs, *N* (%)			
1	4 (8.0)	8 (14.8)	0.81
2	12 (24.0)	10 (18.5)	
3	10 (20.0)	11 (20.4)	
4	13 (26.0)	15 (27.8)	
5 or more	11 (22.0)	10 (18.5)	
Alcohol consumption, *N* (%)	23 (46.0)	28 (52.8)	0.49
Missing	0 (0.0)	1 (1.9)	
Caffeine consumption, *N* (%)	38 (77.8)	44 (83.0)	0.49
Missing	1 (2.0)	1 (1.9)	
Tobacco consumption, *N* (%)	6 (12.0)	13 (24.5)	0.10
Missing	0 (0.0)	1 (1.9)	
Medical history, *N* (%)			
High blood pressure	4 (8.0)	12 (22.2)	0.06
Missing	1 (2.0)	1 (1.9)	
Diabetes	1 (2.0)	1 (1.9)	1.00
Missing	1 (2.0)	1 (1.9)	
Headache	41 (82.0)	49 (90.7)	0.22
Missing	1 (2.0)	1 (1.9)	
Depression	22 (44.0)	21 (38.9)	0.59
Missing	1 (2.0)	1 (1.9)	
Insomnia	39 (78.0)	33 (61.1)	0.09
Missing	1 (2.0)	3 (5.6)	
Anxiety/stress/PTSD	34 (68.0)	36 (66.7)	0.87
Missing	1 (2.0)	1 (1.9)	
Number of comorbidities, *N* (%)[1]			
0	2 (4.0)	2 (3.7)	1.00
1–2	17 (34.0)	18 (33.3)	
3 or more	30 (60.0)	31 (57.4)	
Missing	1 (2.0)	3 (5.6)	

P-values based on chi-squared or Fisher's exact test (categorical variables) and *t*-tests (continuous variables). Missing data categories not included. *P*-values reflect differences between treatment arms for participant characteristics.
[1]Based on observations where no missing data for medical history or use of therapies occur.

Table 4. Number of previous therapeutic modalities tried for mTBI.

Variable	LB group (*N* = 50)	NL group (*N* = 54)	*P*-value
Therapy, *N* (%)	35 (70.0)	31 (57.4)	0.22
Missing	0 (0.0)	1 (1.9)	
Number of therapies, *N* (%)[1]			
0	15 (30.0)	22 (40.7)	0.31
1–2	20 (40.0)	20 (37.0)	
3 or more	14 (28.0)	9 (16.7)	
Missing	1 (2.0)	3 (5.6)	

P-values based on chi-squared or Fisher's exact test (categorical variables) and *t*-tests (continuous variables). Missing data categories not included. *P*-values reflect differences between treatment arms for participant characteristics.
[1]Based on observations where no missing data for medical history or use of therapies occur.

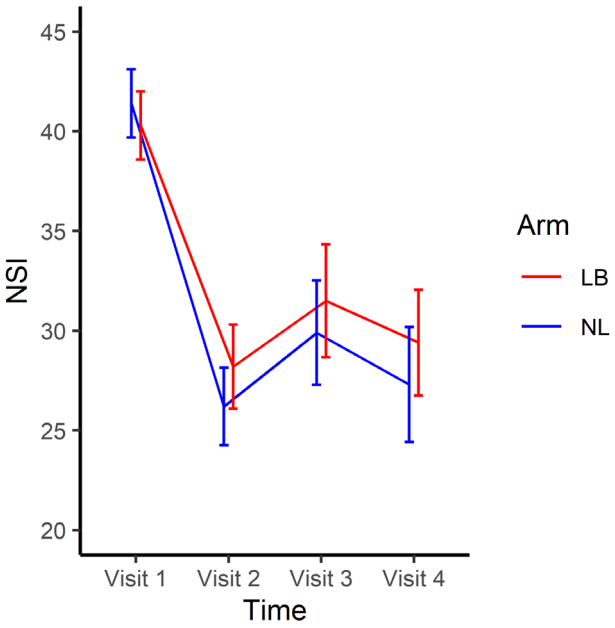

Figure 5. Intention-to-treat outcomes for the Neurobehavioral Symptom Inventory (NSI) (mean ± SE) at baseline (Visit 1), 0–14 days post sessions (Visit 2), 3 months after completion of sessions (Visit 3, primary outcome), and 6 months after completion of sessions (Visit 4) for those receiving intervention (tones linked to brainwaves, LB) compared to control (tones not linked to brainwaves, NL).

shows statistically significant changes from pre-intervention.

Despite the lack of significant benefit of the intervention over sham condition, a drop of 14 points on the NSI in the entire study population is clinically significant and quite remarkable, and was largely sustained out to 6 months post-intervention. Current reliable change for the NSI is 8 points.[46] There has been nothing published in the medical literature that has achieved comparable benefit in reducing postconcussive symptoms. Other interventions, often requiring a much greater time commitment,[47] demonstrated smaller to no notable changes on the NSI.[48] The active sham intervention in this study, acoustic stimulation with engineered tones, does not appear to be a true placebo, as it demonstrated therapeutic value. A reasonable approach would be to try to build on this evidence of response, and particularly to determine why a persistent postconcussive group had a differential response to this intervention compared to other groups. Perhaps for this group dosing of the intervention should be adjusted. Alternatively, the approach for postconcussive symptoms could be simplified, eliminating electrodes and a computer algorithm, using only a zero-gravity chair in a darkened room with acoustic stimulation.

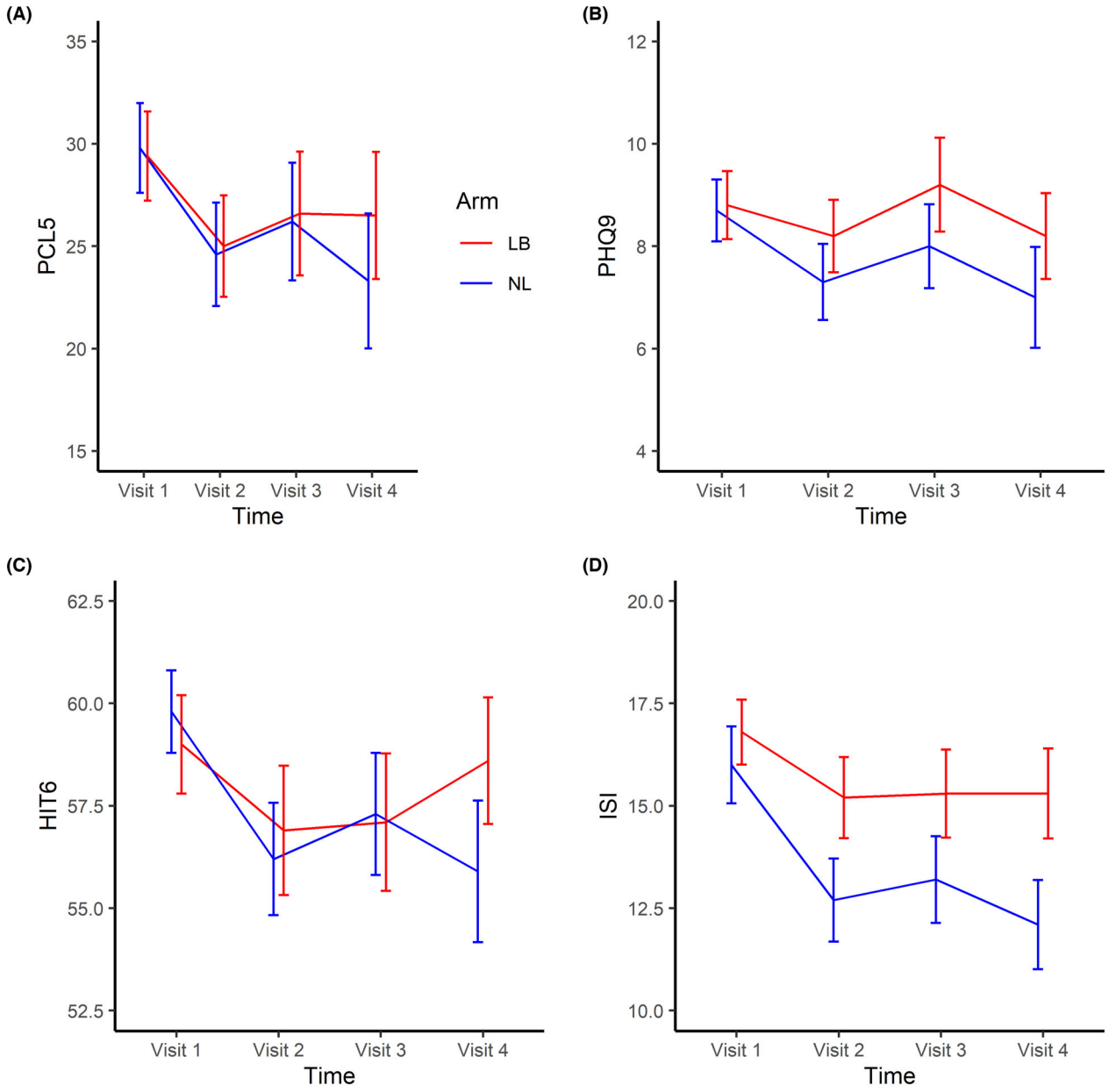

Figure 6. (A–D) Panel of intent-to-treat secondary outcome measures of PTSD Checklist for DSM-5 (PCL5), Patient Health Questionnaire (PHQ9), Headache Impact Test (HIT6), and Insomnia Severity Index (ISI) (mean ± SE) at baseline (Visit 1), 0–14 days post sessions (Visit 2), 3 months after completion of sessions (Visit 3, primary outcome), and 6 months after completion of sessions (Visit 4) for those receiving intervention (tones linked to brainwaves, LB) compared to control (tones not linked to brainwaves, NL).

Growing evidence suggests a therapeutic effect of acoustic stimulation,[49] including for those with TBI. Additionally, music therapy has been demonstrated to affect the autonomic nervous system.[50] Piano playing for 8 weeks resulted in behavioral improvements and functional brain changes on fMRI in a small group with mild TBI.[51] In moderate to severe TBI, music-based neurological rehabilitation improved executive function, and functional connectivity of large scale resting state networks on fMRI.[52] These studies are in keeping with our prior findings of improved network connectivity on fMRI, and improved measures of autonomic function following the use of acoustic neuromodulation (HIRREM) in a cohort with military-related traumatic stress, >80% of whom reported prior TBI.[24,27]

Another approach is to expand the scope of the intervention. We are currently testing the next generation of

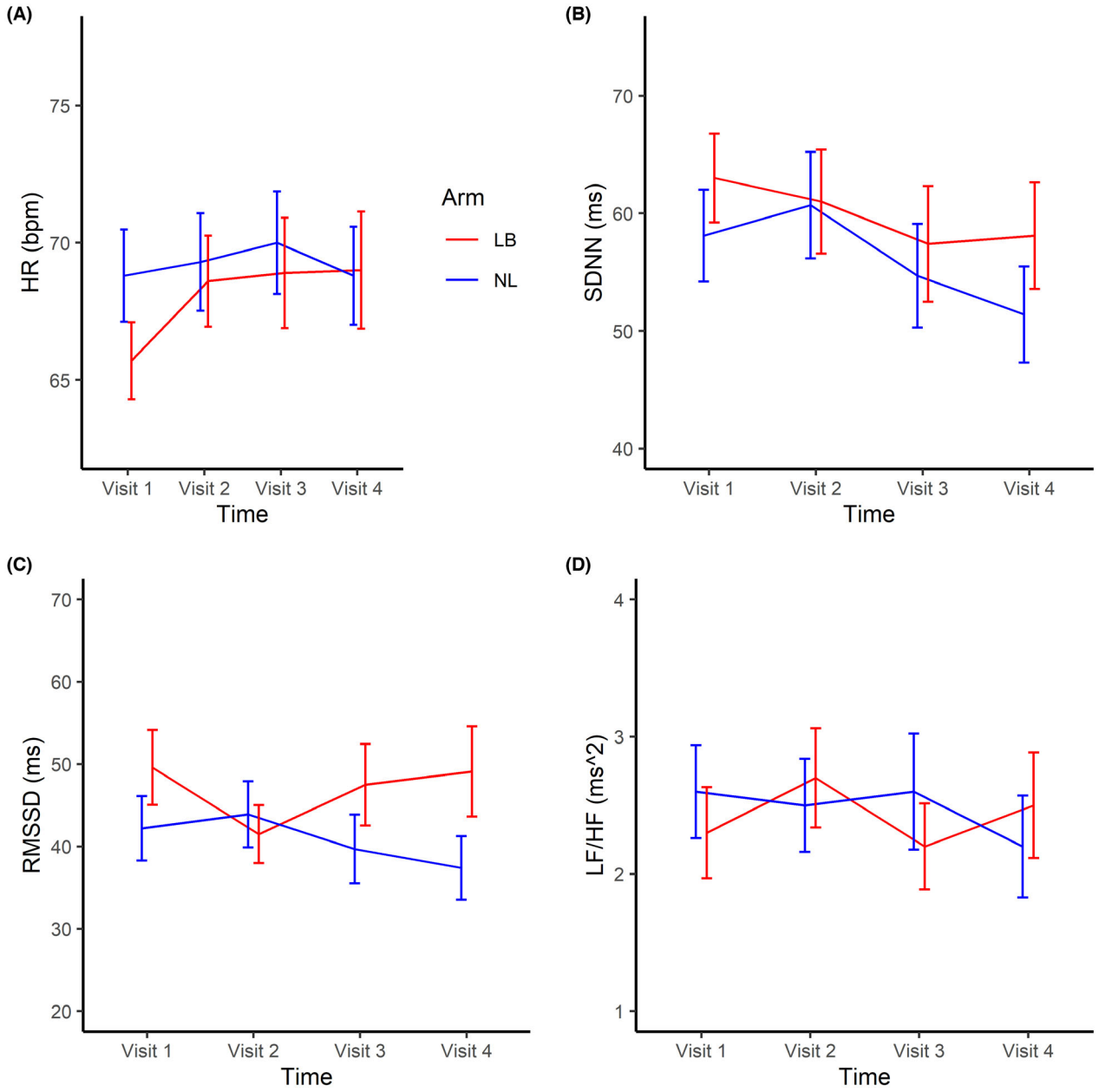

Figure 7. (A–D) Panel of intent-to-treat autonomic functional measures: Heart rate (HR), two heart rate variability outcome measures, RMSSD and SDNN, and LF/HF ratio, a measure of sympathovagal balance. Results (mean ± SE) shown at baseline (Visit 1), 0–14 days post sessions (Visit 2), 3 months after completion of sessions (Visit 3, primary outcome), and 6 months after completion of sessions (Visit 4) for those receiving intervention (tones linked to brainwaves, LB) compared to control (tones not linked to brainwaves, NL).

allostatic neurotechnology which translates brain electrical activity to not only auditory tones, but also very low-level electrical stimulation of the scalp. An elegant series of preclinical and clinical studies[53–59] suggest that highly localized electrical stimulation of the scalp, at levels so low that they are not consciously recognized, can have a significant impact on the brain. We will report these results for mTBI upon the completion of that study.

The brain is complex. There might also be an unexplored relationships between TBI and other neurodegenerative mechanisms.[60] Scientists continue to evaluate if neuroplasticity, inflammation, resonance, or other factors could be influencing the treatment of TBI.

There are potential factors that may have contributed to the inability to demonstrate benefit of the intervention above and beyond the sham condition, and these are

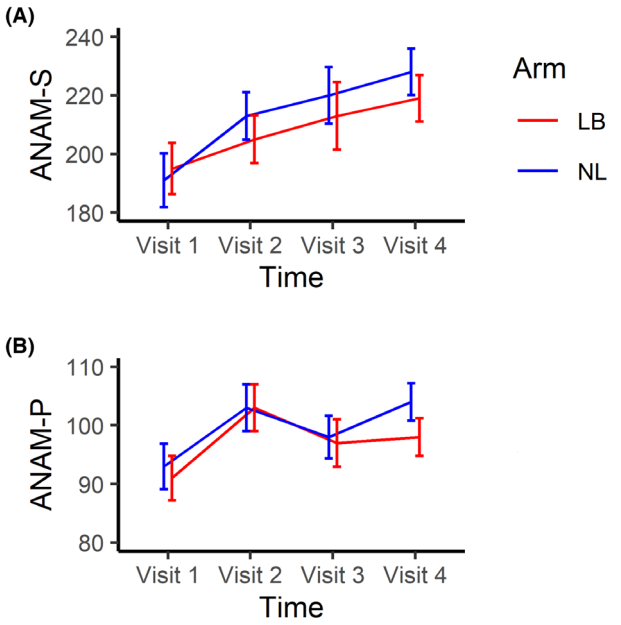

Figure 8. (A, B) Panel of intent-to-treat measure of Automated Neuropsychological Assessment Metrics for simple (ANAM-S) and procedural (ANAM-P) reaction time. Results (mean ± SE) shown at baseline (Visit 1), 0–14 days post sessions (Visit 2), 3 months after completion of sessions (Visit 3, primary outcome), and 6 months after completion of sessions (Visit 4) for those receiving intervention (tones linked to brainwaves, LB) compared to control (tones not linked to brainwaves, NL).

considered limitations of the study. First, the inclusion criteria allowed participants to have had a concussion anywhere between 3 months and 10 years ago. The longer removed from injury, the less likely an individual's symptoms are related to concussion. It is possible if a tighter timeframe was required for enrollment (e.g., 3 months to 1 year), and screening for postconcussive symptoms and comorbid conditions was done such that a "cleaner" postconcussion group was enrolled, the intervention may have been more efficacious. Second, participants were able to complete the intervention over anywhere from 1 to 5 weeks in this study, with a mean of 17.60 days for the LB group. Prior studies that demonstrated a difference between groups had shorter periods of 7.0[30] and 14.78[31] days to complete the intervention. There may be an optimal dosing interval, particularly with more of a bolus over a shorter time frame that might achieve greater benefit, although our analyses did not indicate that response to the intervention in this study was modulated by dosing interval. The military is a unique cohort and researchers have noted how difficult it can be to overcome scheduling challenges.[61] Differential improvement in measures of autonomic function has been a hallmark of prior studies using this technology. Only 65% of participants could be included in analysis of HRV (SDNN) at V3, and 53% at V4. More complete autonomic data might have been better able to identify group differences. Finally, while the primary outcome measure, the NSI, is ostensibly a measure of postconcussive symptoms, there is evidence that it tracks more closely with PTSD symptom severity than with TBI history. In fact, persistent symptoms after mTBI in fact tend to be more closely linked to PTSD.[62] As such, the relaxation elements of the intervention that were common to both arms may have been especially impactful on symptoms of stress.

Conclusions

Participating in a study involving approximately 10 cumulative hours of resting comfortably in a zero-gravity chair in the dark with eyes closed and listening to computer-generated acoustic stimulation is well tolerated and is associated with clinically and statistically significant improvement in postconcussive symptoms. However, the results of this study do not suggest that in a primarily active duty group with postconcussive symptoms listening to acoustic stimulation based on one's own brain electrical activity reduces symptoms, or improves brain function or heart rate variability, more than randomly generated, computer engineered acoustic stimulation. In addition, ongoing work indicates that the combination of acoustic stimulation and microelectrical stimulation of the scalp, also based on brain electrical activity, may have greater power to improve postconcussive symptoms. Future studies will determine if the gains seen in this study can be improved (i.e., greater symptom improvement with fewer treatment sessions) using the combination of acoustic and microelectrical stimulation in a similar noninvasive neurotechnology intervention.

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Author contributions

All authors have reviewed the manuscript and contributed equally.

Conflict of interest

All authors affiliated with the Wake Forest School of Medicine have no conflicts to report. Lee Gerdes is currently employed by Brain State Technologies, Scottsdale, AZ. Wesley Cole completed this work as an employee of the Department of Defense, and is currently employed by the University of North Carolina at Chapel Hill. He has no conflicts of interest to report.

Disclaimers

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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